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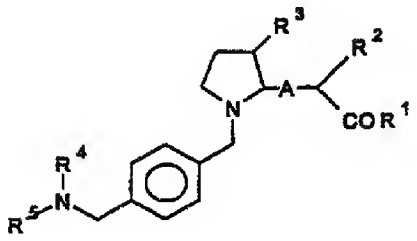
Pyrrolidinepropionic acid derivatives with bradykinin-antagonistic action

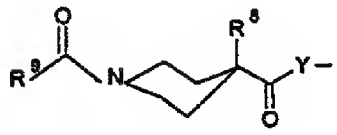
Abstract

Pyrrolidinepropionic acid derivatives of the formula (I)



(I)

with bradykinin-antagonistic activity are described wherein R^1 stands for OH, O-alkyl, O-alkenyl, O-arylalkyl or substituted amine; R^2 stands for alkyl, alkenyl, alkinyl, arylalkyl, cycloalkyl, cycloalkyl-alkyl, cycloalkyl-alkenyl, cycloalkyl-alkinyl, $-(CH_2)_{1-5}-B-(CH_2)_{1-5}-R_5$, aryl; R^3 stands for H, alkyl, cycloalkyl, arylalkyl, alkenyl, alkinyl, R^2 and R^3 together stand for alkyl; R^4 stands for H, alkyl, arylalkyl, alkenyl, -C(O)-O-alkyl, -C(O)-O-alkylaryl, $-C(NH)-NH_2$; A stands for a single or double bond; B stands for O, NR^3 or S; and R^5 stands for H or a residue of the formula II



(II)

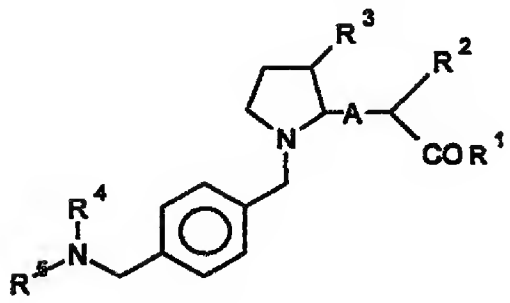
wherein R^8 and R^9 are as defined in the description and Y is a direct bond or an amino acid. A method for the production of the said compound and its use as a therapeutic agent are also described.

Description

The invention relates to non-peptide bradykinin antagonists.

Heterocyclic bradykinin antagonists are described in EP-A-622 361 and US 5,438,064.

The present invention describes pyrrolidinepropionic acid derivatives with bradykinin-antagonistic activity. It relates to compounds of the formula (I)



(I)

wherein the symbols have the following meaning:

a) R^1 stands for

1. –OH,
2. –O–(C_1-C_{10})-alkyl,
3. –O–(C_3-C_6)-alkenyl,
4. –O–(C_6-C_{10})-aryl-(C_1-C_3)-alkyl,
5. $-NR^6R^7$;

b) R^2 stands for

1. (C_1-C_{10})-alkyl,
2. (C_2-C_{10})-alkenyl,
3. (C_3-C_{10})-alkinyl,
4. (C_6-C_{10})-aryl-(C_1-C_3)-alkyl,
5. (C_3-C_8)-cycloalkyl,
6. (C_4-C_{10})-cycloalkyl-(C_1-C_4)-alkyl,
7. (C_5-C_{10})-cycloalkyl-(C_2-C_4)-alkenyl,
8. (C_5-C_{10})-cycloalkyl-(C_2-C_4)-alkinyl,
9. $-(CH_2)_m-B-(CH_2)_n-R^5$,

10. $(C_6\text{-}C_{10})$-aryl,

11. a residue as defined in b) 1., 2., 3. or 9. which is monosubstituted with COR^1,

12. a residue as defined in b) 1., 2., 3. or 9. wherein one to all the H atoms are substituted by halogen, or

13. the residue defined in b) 4. and 10. substituted on the aryl by 1 or 2 of the same or different residues from the series halogen, $(C_1\text{-}C_4)$-alkoxy and nitro, cyano;

c) R^3 stands for

1. hydrogen,

2. $(C_1\text{-}C_8)$-alkyl,

3. $(C_3\text{-}C_8)$-cycloalkyl,

4. $(C_6\text{-}C_{10})$-aryl-$(C_1\text{-}C_3)$-alkyl,

5. $(C_2\text{-}C_6)$-alkenyl,

6. $(C_3\text{-}C_6)$-alkinyl,

7. R^2 and R^3 together stand for $(C_2\text{-}C_4)$-alkyl,

8. a residue as defined in c) 7. which is substituted by halogen;

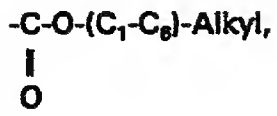
d) R^4 stands for

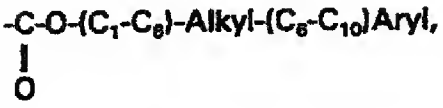
1. hydrogen,

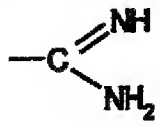
2. $(C_1\text{-}C_6)$-alkyl,

3. $(C_6\text{-}C_{10})$-aryl-$(C_1\text{-}C_3)$-alkyl,

4. $(C_3\text{-}C_{10})$-alkenyl,

5. 

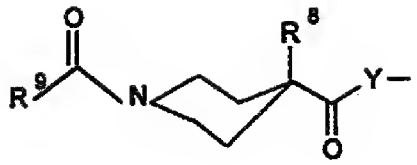
6. 

7. 

e) R^5 stands for

1. hydrogen,

2. a residue of the formula (II)



(II)

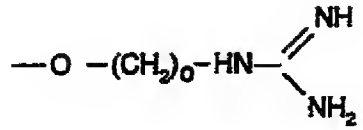
f) R^6 and R^7 are the same or different and stand for

1. hydrogen,
2. $(C_1\text{-}C_{10})$-alkyl,
3. $(C_6\text{-}C_{10})$-aryl-$(C_1\text{-}C_3)$-alkyl,
4. $(C_1\text{-}C_{10})$-alkylamino,
5. $(C_1\text{-}C_{10})$-alkylguanidino;

g) R^8 stands for

1. $(C_6\text{-}C_{10})$-aryl,
2. $(C_1\text{-}C_6)$-alkyl,
3. $(C_3\text{-}C_8)$-cycloalkyl,
4. $(C_6\text{-}C_{10})$-aryl-$(C_1\text{-}C_3)$-alkyl,
5. $(C_2\text{-}C_6)$-alkenyl,
6. a residue defined in g) 1. and 4. which is substituted with one or more residues from the series COR^1, halogen, nitro, cyano, $(C_1\text{-}C_4)$-alkoxy or amino;

h) R^9 stands for

1. $–NH–(CH_2)_o–NHR^4$
2. $–O–(CH_2)_o–NH_2$
3. 

i) A stands for a single or double bond;

j) B is O, NR^3 or S;

k) Y stands for a direct bond or an amino acid, preferably phenylalanine, 2-chlorophenylalanine, 3-chlorophenylalanine, 4-chlorophenylalanine, 2-fluorophenylalanine, 3-fluorophenylalanine, 4-fluorophenylalanine, tyrosine, O-methyltyrosine, β-(2-thienyl)alanine, glycine, cyclohexylalanine, leucine, isoleucine, valine, norleucine or phenylglycine, serine or cysteine;

l) m stands for a number from 1 to 5,

m) n stands for a number from 1 to 5,

n) o stands for a number from 1 to 10,

and physiologically compatible salts thereof.

Alkyl, alkenyl and alkinyl can be straight-chain or branched. The same applies to residues derived therefrom, e.g. alkoxy.

By cycloalkyl are also meant rings substituted by (C_1-C_8)-alkyl.

(C_6-C_{12})-aryl is for example phenyl, naphthyl or biphenylyl, preferably phenyl. The same also applies to residues derived therefrom, e.g. aralkyl.

Halogen stands for fluorine, chlorine, bromine or iodine, preferably chlorine.

By physiologically compatible salts of compounds of formula (I) are meant both organic and inorganic salts thereof, as are described in Remington's Pharmaceutical Sciences (17^{th} edition, page 1418 (1985)). Acid groups, *inter alia* sodium salts, potassium salts, calcium salts and ammonium salts, are preferred owing to their physical and chemical stability and solubility; for basic groups, salts of hydrochloric acid, sulphuric acid, phosphoric acid or of carboxylic acids or sulphonic acids, e.g. acetic acid, citric acid, benzoic acid, maleic acid, fumaric acid, tartaric acid and p-toluenesulphonic acid, are preferred *inter alia*.

Compounds of formula I are preferred wherein

a) R^2 stands for

1. (C_1-C_6)-alkyl,
2. (C_2-C_6)-alkenyl,
3. (C_6-C_{10})-aryl-(C_1-C_3)-alkyl,
4. (C_3-C_8)-cycloalkyl,
5. (C_3-C_6)-cycloalkyl-(C_1-C_3)-alkyl,

6. a residue defined in a) 3. and 5. which is substituted with one or more residues from the series halogen, nitro, cyano (C_1-C_4)-alkoxy, COR^1 or amino;

c) R^8 stands for

1. (C_6-C_{10})-aryl,
2. (C_6-C_{10})-aryl-(C_1-C_3)-alkyl,
3. a residue defined in c) 1. and 2. which is substituted with one or more residues from the series halogen, nitro, cyano, (C_1-C_4)-alkoxy, amino or COR^1;

and wherein the other residues are substituted as above.

Very particularly preferred are compounds of the formula (I) wherein

a) R^1 stands for –O–(C_1-C_{10})-alkyl;

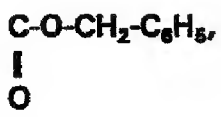
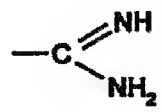
b) R^2 stands for

1. (C_6-C_{10})-aryl-CH_2–,
2. (C_3-C_8)-cycloalkyl,
3. (C_3-C_8)-cycloalkyl-CH_2–;

c) R^3 stands for

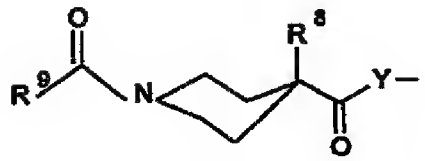
1. (C_3-C_5)-alkenyl,
2. phenyl-(C_1-C_3)-alkyl,
3. R^2 and R^3 together stand for (C_2-C_3)-alkyl;

d) R^4 stands for

1. hydrogen,
2. 
3. 
4. 

e) R^5 stands for

1. hydrogen,
2. a residue of the formula (II)

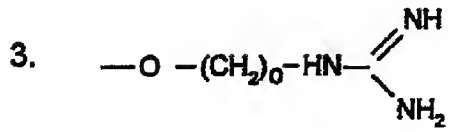


(II)

f) R^8 stands for

1. phenyl,
2. benzyl;

g) R^9 stands for

1. $-NH-(CH_2)_o-NHR^4$,
2. $-O-(CH_2)_o-NH_2$,
3. 

h) A is a single or double bond;

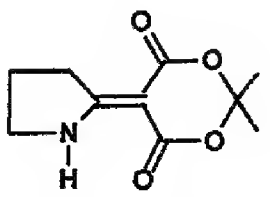
i) Y stands for

1. a single bond,
2. an amino acid from the series phenylalanine, β-(2-thienyl)alanine, O-methyltyrosine, glycine, cyclohexylalanine, leucine, isoleucine, valine, phenylglycine, serine or cysteine;

j) o is a number from 1 to 10.

The invention relates also to a method for the production of compounds of the formula I, characterised in that

a) a compound of the formula (III)



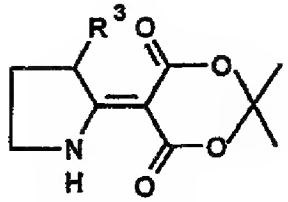
(III)

with a compound R^3-X wherein

R^3 stands for hydrogen, (C_1-C_8)-alkyl, (C_3-C_8)-cycloalkyl, (C_6-C_{10})-aryl-(C_1-C_3)-alkyl, (C_2-C_6)-alkenyl or (C_3-C_6)-alkinyl, and

X stands for a leaving group, such as halogen, mesylate or tosylate,

is reacted with an organometallic base, such as n-butyllithium, s-butyllithium, methyllithium or phenyllithium, sodium amide and alkali-metal salts of organic nitrogen bases, such as lithium diisopropylamide, in an inert solvent such as THF, ether, toluene or dimethoxyethane, preferably at -78°C, to form a compound of the formula IV



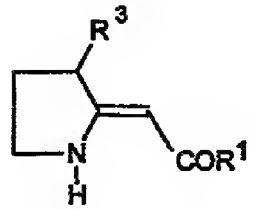
(IV)

wherein R^3 is as defined above;

b) the compound of formula IV is boiled under reflux with an alcoholate of the formula R^1Na or R^1K wherein

R^1 stands for –OH, –O–(C_1-C_{10})-alkyl, O–(C_3-C_6)-alkenyl or –O–(C_6-C_{10})-aryl-(C_1-C_3)-alkyl,

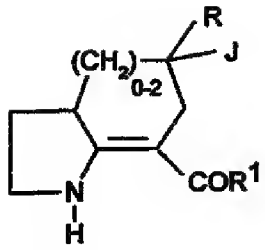
and the corresponding alcohol, a compound of the formula V being obtained



(V)

wherein R^1 and R^3 are as defined above;

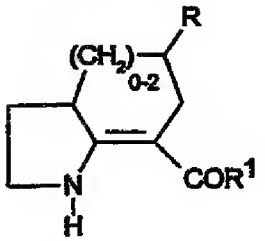
c_1) if in formula I R^2 and R^3 together stand for (C_2-C_4)-alkyl which may optionally be substituted with halogen and in formula V R^3 stands for (C_2-C_6)-alkenyl, the compound of formula V is reacted with J_2 or radical-producing reagents in methylene chloride or THF at room temperature to form a compound of the formula VI



(VI)

wherein R stands for hydrogen or (C_1-C_3)-alkyl and R^1 is as defined in b), and

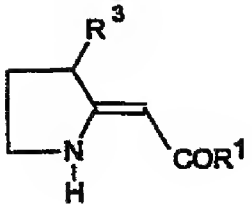
c_2) the resultant compound of formula VI is reacted with Raney nickel at 1 atm H_2 and diisopropylethylamine as base for 1 hour at room temperature to form a compound of the formula VII



(VII)

wherein R stands for hydrogen or (C_1-C_3)-alkyl and R^1 is as defined in b);

d) if in formula I R^2 and R^3 together do not stand for (C_2-C_4)-alkyl which may optionally be substituted with halogen, a compound of the formula V



(V)

wherein R^1 stands for –O–(C_1-C_{10})-alkyl, –O–(C_3-C_6)-alkenyl or –O–(C_6-C_{10})-aryl-(C_1-C_3)-alkyl and

R^3 stands for hydrogen, (C_1-C_8)-alkyl, (C_3-C_8)-cycloalkyl, (C_6-C_{10})-aryl-(C_1-C_3)-alkyl, (C_2-C_6)-alkenyl or (C_3-C_6)-alkinyl

is deprotonated with a base, e.g. sodium hydride, and is then reacted with a compound R^2–X,

wherein R^2 stands for (C_1-C_{10})-alkyl, (C_2-C_{10})-alkenyl, (C_3-C_{10})-alkinyl, (C_6-C_{10})-aryl-(C_1-C_3)-alkyl, (C_3-C_8)-cycloalkyl, (C_4-C_{10})-cycloalkyl-(C_1-C_4)-alkyl, (C_5-C_{10})-cycloalkyl-(C_2-C_4)-alkenyl, (C_5-C_{10})-cycloalkyl-(C_2-C_4)-alkinyl,

$(CH_2)_m$–B–$(CH_2)_n$–R^5, $(C_6$-$C_{10})$-aryl; $(C_1$-$C_{10})$-alkyl, $(C_2$-$C_{10})$-alkenyl, $(C_3$-$C_{10})$-alkinyl or –$(CH_2)_m$–B–$(CH_2)_n$–R^5 which are monosubstituted with COR^1; $(C_1$-$C_{10})$-alkyl, $(C_2$-$C_{10})$-alkenyl, $(C_3$-$C_{10})$-alkinyl or $(CH_2)_m$–B–$(CH_2)_n$–R^5 wherein one to all the H atoms are substituted by halogen; or $(C_6$-$C_{10})$-aryl-$(C_1$-$C_3)$-alkyl or $(C_6$-$C_{10})$-aryl which are substituted on the aryl with 1 or 2 of the same or different residues from the series halogen, $(C_1$-$C_4)$-alkoxy and nitro, cyano,

B is O, NR^3 or S,

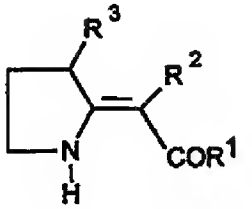
m is a number from 1 to 5,

n is a number from 1 to 5,

R^5 stands for hydrogen or a residue of the formula II, and

X stands for a suitable leaving group, e.g. halogen, mesylate or tosylate,

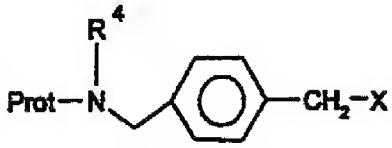
to form a compound of the formula VIII



(VIII)

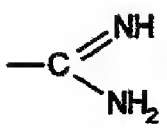
wherein R^1, R^2 and R^3 are as defined in d);

e) the compound of formula VIII with a compound of the formula



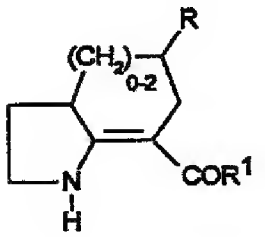
wherein Prot stands for an amino protective group, e.g. tert. butoxycarbonyl,

R^4 is hydrogen, $(C_1$-$C_6)$-alkyl, $(C_6$-$C_{10})$-aryl-$(C_1$-$C_3)$-alkyl, $(C_3$-$C_{10})$-alkenyl, –C(O)–O–$(C_1$-$C_6)$-alkyl, –C(O)–O–$(C_1$-$C_6)$-alkyl-$(C_6$-$C_{10})$-aryl, or

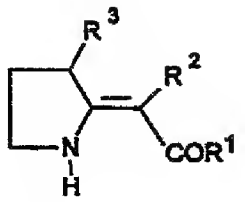


and X stands for a suitable leaving group, e.g. halogen, mesylate or tosylate,

is deprotonated with a base, e.g. sodium hydride, and is then reacted with a compound of the formula VII or VIII



(VII)



(VIII)

wherein R stands for hydrogen or $(C_1\text{-}C_3)$-alkyl,

R^1 is as defined in d),

R^2 stands for $(C_1\text{-}C_{10})$-alkyl, $(C_2\text{-}C_{10})$-alkenyl, $(C_3\text{-}C_{10})$-alkinyl, $(C_6\text{-}C_{10})$-aryl-$(C_1\text{-}C_3)$-alkyl, $(C_3\text{-}C_8)$-cycloalkyl, $(C_4\text{-}C_{10})$-cycloalkyl-$(C_1\text{-}C_4)$-alkyl, $(C_5\text{-}C_{10})$-cycloalkyl-$(C_2\text{-}C_4)$-alkenyl, $(C_5\text{-}C_{10})$-cycloalkyl-$(C_2\text{-}C_4)$-alkinyl, $(CH_2)_m\text{–}B\text{–}(CH_2)_n\text{–}R^5$, $(C_6\text{-}C_{10})$-aryl; $(C_1\text{-}C_{10})$-alkyl, $(C_2\text{-}C_{10})$-alkenyl, $(C_3\text{-}C_{10})$-alkinyl or $\text{–}(CH_2)_m\text{–}B\text{–}(CH_2)_n\text{–}R^5$ which are monosubstituted with COR^1; $(C_1\text{-}C_{10})$-alkyl, $(C_2\text{-}C_{10})$-alkenyl, $(C_3\text{-}C_{10})$-alkinyl or $(CH_2)_m\text{–}B\text{–}(CH_2)_n\text{–}R^5$ wherein one to all the H atoms are substituted by halogen; or $(C_6\text{-}C_{10})$-aryl-$(C_1\text{-}C_3)$-alkyl or $(C_6\text{-}C_{10})$-aryl which are substituted on the aryl with 1 or 2 of the same or different residues from the series halogen, $(C_1\text{-}C_4)$-alkoxy and nitro, cyano,

B is O, NR^3 or S,

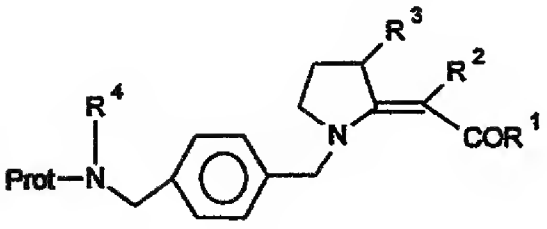
m is a number from 1 to 5,

n is a number from 1 to 5,

R^5 stands for hydrogen or a residue of the formula II, and

R^3 stands for hydrogen, $(C_1\text{-}C_8)$-alkyl, $(C_3\text{-}C_8)$-cycloalkyl, $(C_6\text{-}C_{10})$-aryl-$(C_1\text{-}C_3)$-alkyl or $(C_3\text{-}C_6)$-alkinyl,

to form a compound of the formula IX



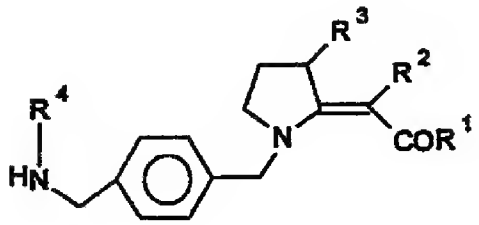
(IX)

wherein R^1, R^2, R^3, R^4 and Prot are as defined in e) and

R^2 and R^3 together stand for $(C_2\text{-}C_4)$-alkyl optionally substituted with halogen;

f) the amino protective group Prot is cleaved off by known methods, e.g. with tert. butoxycarbonyl (Boc) under acidic conditions, preferably in trifluoroacetic acid (TFA) or with HCl in dimethoxyethane, or with TFA in dimethoxyethane or dichloromethane as preferred solvent;

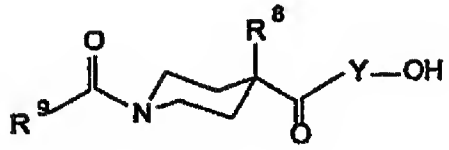
g) optionally the resultant compound of formula X with a free amino group



(X)

wherein R^1, R^2, R^3 and R^4 are as defined in e) (formula IX),

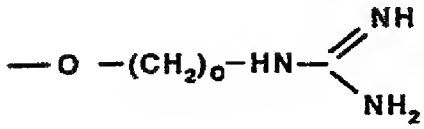
is coupled according to the general methods of peptide chemistry with a compound of the formula II'



(II')

wherein R^8 stands for (C_6-C_{10})-aryl, (C_1-C_6)-alkyl, (C_3-C_8)-cycloalkyl, (C_6-C_{10})-aryl-(C_1-C_3)-alkyl, (C_2-C_6)-alkenyl; (C_6-C_{10})-aryl or (C_6-C_{10})-aryl-(C_1-C_3)-alkyl substituted with one or more residues from the series COR^1, halogen, nitro, cyano, (C_1-C_4)-alkoxy or amino,

R^9 stands for $–NH–(CH_2)_o–NHR^4$, $–O–(CH_2)_o–NH_2$ or

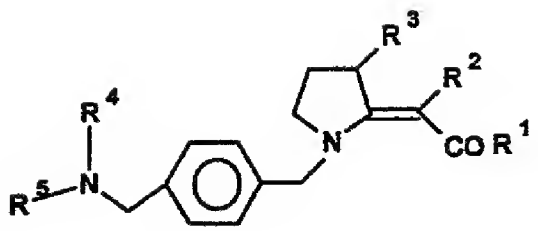


R^4 is as defined in e),

o is a number from 1 to 10, and

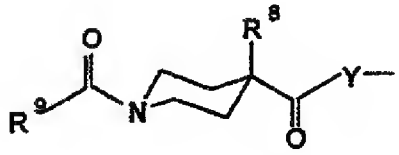
Y stands for a direct bond or an amino acid,

so that a compound of formula X' is obtained



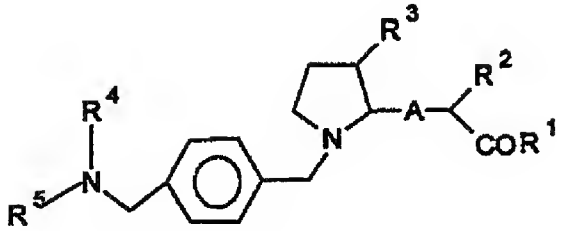
(X')

wherein R^1, R^2, R^3 and R^4 are as defined in g) and R^5 stands for



wherein R^8, R^9 and Y are as defined in g);

h) optionally the double bond of the formulae X or X' is hydrogenated with sodium cyanoborohydride in lower alcohols, such as methanol, at room temperature and around pH 5 to a compound of the formula XI



(XI)

wherein R^1, R^2, R^3, R^4 and R^5 are as defined in g) and

A stands for a single bond;

i) optionally the compounds of the formulae X, X' or XI are saponified under acidic or basic conditions or are heated with HNR^6R^7,

wherein R^6 and R^7 are the same or different and stand for hydrogen, $(C_1\text{-}C_{10})$-alkyl, $(C_6\text{-}C_{10})$-aryl-$(C_1\text{-}C_3)$-alkyl, $(C_1\text{-}C_{10})$-alkylamino or $(C_1\text{-}C_{10})$-alkylguanidino,

in high-boiling solvents, e.g. xylene or DMF, the compounds of formula I being obtained; and

k) the compounds of the formula I are optionally converted by known methods to their physiologically compatible salts.

The amide bond from fragment X and II' is formed by reacting a fragment with a C-terminal free carboxyl group or its activated derivative with a corresponding fragment with an N-terminal free amino group and in the compound obtained optionally cleaving off one or more protective groups temporarily introduced to protect other functions and optionally converting the resultant compounds of formula I into their physiologically compatible salt.

Coupling of the amino acids of the present invention was conducted in accordance with generally known methods of peptide chemistry, see for example Houben-Weyl, Methoden der organischen Chemie [*Methods of organic chemistry*], Volume 15/2, Stuttgart 1974.

The functional groups of the amino acids are protected by suitable protective groups (see for example T.W. Greene, "Protective Groups in Organic Synthesis", John Wiley, 2nd edition, 1991) to prevent side reactions or for the synthesis of special peptides.

Coupling reagents that may be used are all possible activation reagents used in peptide chemistry, see e.g. Houben-Weyl, Methoden der organischen Chemie, Volume 15/2, Stuttgart, 1974, in particular carbodiimides such as N,N'-dicyclohexylcarbodiimide, N,N'-diisopropylcarbodiimide or N-ethyl-N'-(3-dimethyl-aminopropyl)carbodiimide. Coupling can be performed directly by addition of amino acid derivative with the activation reagent and optionally by an addition that suppresses racemisation such as 1-hydroxybenzotriazole (HOBt) (W. König, R. Geiger, Chem. Ber. 103, 708 (1970)) or 3-hydroxy-4-oxo-3,4-dihydrobenzotriazine (HOObt) (W. König, R. Geiger, Chem. Ber. 103, 2054 (1970)), or the amino acid derivative as a symmetrical anhydride or HOBt or HOObt ester can be pre-activated separately and the solution of the activated species in a suitable solvent can be added to the coupleable amine.

Coupling and/or activation of the amino acid derivatives with one of the above-mentioned activation reagents can be performed in dimethylformamide, N-methylpyrrolidone or methylene chloride or a mixture of the said solvents.

Coupling of the Boc-protected diamines to the piperidine derivatives to form a urea functionality is preferably done using carbodiimides, phosgene or chloroformic acid ester as activated carbonyl reagents.

Starting from the corresponding amines, guanidino derivatives are synthesised with reagents that transfer the amidino group, preferably 1-H-pyrazolecarboxamidine.

The compounds according to the invention have, individually or in combination, bradykinin-antagonistic activity which can be tested in various models (see Handbook of Exp. Pharmacol., Vol. 25, Springer Verlag, 1970, pp. 53-55), for example in isolated rat uterus, guinea-pig ileum or isolated guinea-pig pulmonary artery.

Measurement of binding to the bradykinin B_2 receptor of guinea-pig ileum is described hereinafter (R.B. Innis et al., Proc. Natl. Acad. Sci. USA; 17 (1981) 2630):

1. Ligand: ^{3}H-BRADYKININ (from NEN Du Pont)
2. Buffers:

a) TES buffer:

25 mM TES (SIGMA, order no.: T-4152)

1 mM 1,10-phenanthroline (SIGMA, order no.: P-9375)

b) Incubation buffer:

25 mM TES (SIGMA, order no.: T-4152)

1 mM 1,10-phenanthroline (SIGMA, order no.: P-9375)

0.1% albumin, bovine (SIGMA, order no.: A-7906)

140 µg/ml bacitracin (SIGMA, order no.: B-0125)

1 mM dithiothreitol (SIGMA, order no.: D-0632)

1 µM captopril → 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline

Both buffers are adjusted to pH 6.8 with 5 mol NaOH.

3. Membrane preparation:

Guinea-pig ilea are coarsely freed from the contents of the intestine by careful stripping and cleaned in 0.9% NaCl solution.

The approx. 2 cm long sections of ilea are transferred to ice-cold TES buffer (approx. 1 g/10 ml) and homogenised in an ice bath for approx. 30 sec with the Ultra-Turrax.

The homogenate is then filtered through 3 layers of gauze and the filtrate centrifuged at 50,000 g for 10 minutes.

The supernatant is discarded, the pellet rehomogenised in the same volume of TES buffer and centrifuged again at 50,000 g for 10 minutes.

The pellet is rehomogenised in the incubation buffer (approx. 1 g/5 ml) and frozen in 2 ml portions in cryo tubes at -70°C.

The protein concentration of the finished membrane suspension is determined in accordance with LOWRY and should be around 15 µg/100 µl.

4. Binding test:

All incubations are carried out at room temperature for 60 minutes on microtitre plates (96 x 300 µl) in 200 µl volumes. All batches in incubation buffer. To this end, 50 µl of the radioligand, 50 µl of the preparation to be tested and 100 µl of the membrane suspension are pipetted one after the other into the wells of the microtitre plate.

a) Saturation experiments (hot saturation):

Production of ^{3}H-bradykinin solution: The concentrations 0.05, 0.1, 0.2, 0.4, 0.6, 0.8, 1.0, 1.5, 2.0, 2.5 and 3.0 nmol/l, corresponding to 0.05 to 3.0 pmol/ml, are used for the saturation experiments. After producing the corresponding dilutions, 50 µl of each is added per sample.

Non-specific binding: Non-specific binding must be determined for each concentration of the radioactive ligand. This can be done by adding a high concentration (1-100 µmol) of the non-labelled ligand, other antagonists or agonists of the bradykinin receptor. Hoe 140 (10 µmol/l) is used in this test. To this end, 1.862 mg is dissolved in 1 ml dimethylsulphoxide (DMSO), diluted 1:25 with incubation buffer and 50 µl of this solution added to the samples in the microtitre plate. The reaction is started by adding 100 µl of the membrane suspension.

b) Competition experiments (IC_{50}):

A fixed amount of the radioactive ligand (0.25 to 0.3 nmol/l ^{3}H-bradykinin) and various concentrations of non-labelled agonists or antagonists are used here. 50 µl of the preparations to be tested or standards in the concentrations 10^{-5} to 10^{-10} mol/l are each added to 50 µl of the ^{3}H-bradykinin solution and the reaction started by adding 100 µl of membrane suspension. Triple determinations are carried out in this test too, and three samples are incubated with 10 µmol/l Hoe 140 to determine non-specific binding.

The preparations to be tested for competition are essentially dissolved in dimethylsulphoxide (DMSO) in a concentration of 1 mmol/l, and then further diluted with DMSO. This solution is then diluted 1:25 with incubation buffer.

Following incubation the samples are filtered in a Skatron cell harvester over Whatmann GF/B filter paper strips presoaked with 0.1% PEI (polyethyleneimine) and then each sample washed with 10 ml ice-cold TES buffer. The still damp filters are punched out in mini scintillation tubes and filled with 3 ml scintillator. After approximately 12 hours soaking time the samples are briefly shaken and measured in the beta counter.

c) Screening:

Only one or two concentrations of the test preparation (10^{-5} and 10^{-6} mol/l) are generally used in the primary screening. If displacement of the radioligand by 50% or more is detected at the highest concentration, a full analysis (competition experiment) is carried out with at least 8 concentrations.

4. Evaluation:

The evaluation is performed by the LIGAND program package (McPherrson, Minson & Rodbard, distributor: Elsevier-BIOSOFT) which does the necessary calculations for determining IC_{50} and K_i values. This program also undertakes graphic representations of the saturation and displacement curves, as well as the SCATCHARD plot, HILL plot and HOFSTEE plot.

Determination of the antagonistic effect on bradykinin-induced contraction of guinea-pig ileum is carried out in accordance with the following protocol:

Guinea-pigs weighing approx. 300 g (Morioth strain, ♂, ♀) are killed by a rabbit punch and exsanguinated. A length of approx. 20 cm ileum is prepared, rinsed with Tyrode's solution (recording syringe) and in this way freed from the contents of the intestine. It is then divided into 1.5 cm long sections. These are fixed in 10 ml organ baths filled with Tyrode's solution and joined with expansion measuring strips (isometric contraction measurement). The preload is 1 g. The Tyrode's solution is heated in a water bath to 37°C and bubbled through with compressed air.

After an interval of 30 min. the experiment begins. After plotting the biological zero line bradykinin in a final concentration of 4×10^{-8} mol/l is added to each organ bath and the concentration plotted. Washing with Tyrode's solution for 3 min. then takes place and after an interval of 20 min. bradykinin is added again. The contraction maximum is attained (control). Then washing and rest period again. The bradykinin

antagonist is now added (allowed to act for 10 min.). Thereafter bradykinin is added again and the contraction that then takes place is compared with that of the control. The experiment is plotted on a chart recorder.

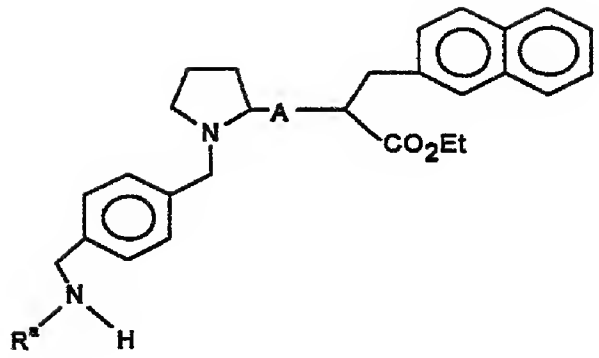
Tyrode's solution (mM):

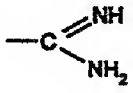
NaCl	137
Glucose	5.05
KCl	2.68
$NaHCO_3$	11.9
NaH_2PO_4	0.47
$MgCl_2 \times 2H_2O$	0.49
$CaCl_2 \times 2H_2O$	0.68

Amplifier: TF6 V3, Fleck, Mainz
Chart recorder: Goerz Metrawatt SE 460, BBC
Bradykinin: Bachem

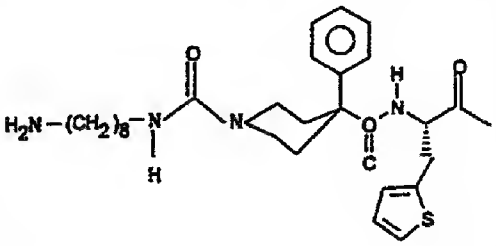
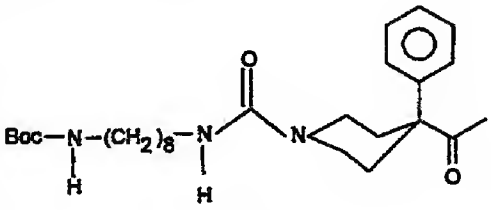
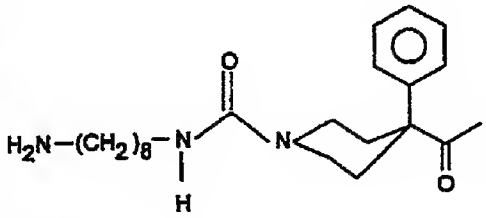
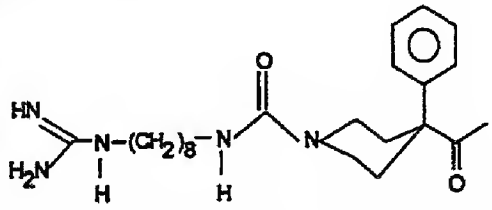
Table 1*

Biological data

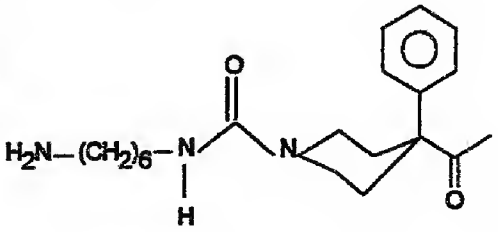
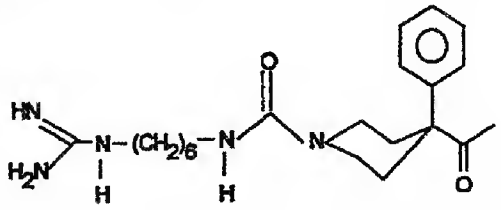


Beispiel	A	R*	Ki(μm)[1]	IC_{50} GPI[μM][2]
1	Einfach-bindung	Boc	3.7	–
2	Doppel-bindung	H	14.0	3.2
3	Einfach-bindung	H	7.2	2.0
4	Doppel-bindung		1.9	1.5
5	Einfach-bindung	〃	3.0	0.3

[Beispiel = *example*, Einfachbinding = *single bond*, Doppelbinding = *double bond*]

Beispiel	A	R*	Ki(μm)[1]	IC_{50} GPI[μM][2]
6	Doppelbindung		3.5	10.0
7	Einfachbindung	"	3.7	6.9
8	Doppelbindung		–	7.6
9	Einfachbindung	"	6.6	22.0
10	Doppelbindung		–	–
11	Einfachbindung	"	–	5.8
12	Doppelbindung		1.7	–

[Beispiel = *example*, Einfachbinding = *single bond*, Doppelbinding = *double bond*]

Beispiel	A	R^a	Ki(µm)[1]	IC_{50} GPI[µM][2]
13	Einfach-bindung	"	1.6	0.17
14	Doppel-bindung		–	–
15	Einfach-bindung	"	2.4	–
16	Einfach-bindung		7.4	2.0

[Beispiel = *example*, Einfachbinding = *single bond*, Doppelbinding = *double bond*]

* The structures of the examples are shown as free bases.

$R^a = R^4$ or R^5

[1]) Measured on guinea-pig ileum B_2 receptor.

[2]) Antagonistic effect of the examples against bradykinin-induced contraction of guinea-pig ileum.

For the oral administration form or for application to mucous membranes, the active compounds are mixed with conventional additives such as vehicles, stabilisers or inert diluents and made into suitable dosage forms, e.g. tablets, coated tablets, hard capsules, aqueous, alcoholic or oily suspensions or aqueous, alcoholic or oily solutions, by conventional methods. Inert vehicles that can be used are, for example, gum arabic, magnesium oxide, magnesium carbonate, potassium phosphate, lactose, glucose, magnesium stearyl fumarate or starch, particularly maize starch. The preparation can be in the form of both dry granules and wet granules. Possible oily

vehicles or solvents are, for example, vegetable or animal oils such as sunflower oil and cod-liver oil.

A preparation for topical application may be in the form of an aqueous or oily solution, lotion, emulsion or gel, unguent or ointment, or if possible, in spray form, adhesion optionally being improved by the addition of a polymer.

For the intranasal form of administration the compounds are mixed with conventional additives such as stabilisers or inert diluents and made into suitable dosage forms, e.g. aqueous, alcoholic or oily suspensions or aqueous, alcoholic or oily solutions, by conventional methods. To aqueous intranasal preparations there can be added chelating agents, ethylenediamine-N,N,N',N'-tetraacetic acid, citric acid, tartaric acid or salts thereof. Nasal solutions can be administered by means of a metered-dose atomiser or as nasal drops with a viscosity-increasing moiety or by means of a nasal gel or nasal cream.

The therapeutic benefit of the compounds according to the invention covers all pathological conditions mediated, triggered or supported by bradykinin and bradykinin-related peptides. This includes for example trauma, such as wounds, burns, rashes, erythema, oedema, angina, arthritis, asthma, allergies, rhinitis, shock, inflammation, pancreatitis, arteriosclerosis, viral diseases, low blood pressure, pain, pruritus and altered sperm motility.

The invention therefore relates also to the use of compounds of formula I as therapeutic agents and pharmaceutical preparations containing the said compounds.

Pharmaceutical preparations contain an effective quantity of the active ingredient of formula I – alone or in combination – together with an inorganic or organic pharmaceutically useable vehicle.

Administration can be by the enteric, parenteral – e.g. subcutaneous, i.m. or i.v. – sublingual, cutaneous, nasal, rectal, intravaginal or intrabuccal route or by inhalation. The dose of the active ingredient depends on the mammal species, bodyweight, age and method of administration.

The pharmaceutical preparations of the present invention are produced by known dissolution, mixing, granulation or coating methods.

Nebulisers or compressed gas packs using inert carrier gases can be employed for administration by inhalation.
For intravenous, subcutaneous, cutaneous or intradermal administration the active compounds or their physiologically compatible salts, optionally with pharmaceutically conventional excipients, for example for isotonisation or pH adjustment, and solubility promoters, emulsifiers or other excipients are brought into solution, suspension or emulsion.

Owing to the short half-lives of some of the described medicines in body fluids, the use of injectable sustained-release preparations is sensible. Dosage forms that can be used are e.g. oily crystal suspensions, microcapsules, rods or implants, the latter being constructed from tissue-compatible polymers, particularly biodegradable polymers, e.g. based on polylactic acid/polyglycolic acid copolymers or human albumin.

A suitable dosing range for topical and inhaled forms of administration is 0.01-5 mg/ml for solutions and 0.01-10 mg/kg for systemic forms.

The abbreviations used for amino acids correspond to the conventional three-letter code in peptide chemistry, as described in Europ. J. Biochem. 138, 9 (1984). Other abbreviations used are listed below:
Cha: cyclohexylalanine
Nle: norleucine
Oic: 2S, 3aS, 7aS-hexahydro-2-indolinyl carboxylic acid
Phg: phenylglycine
Ser(t-but): O-tert.-butyl-L-serine
D-Tic R-1,2,3,4-tetrahydro-3-isoquinolyl carboxylic acid
Thi: L-β(2-thienyl)alanine
Boc: t-butyloxycarbonyl
CH_2Cl_2: dichloromethane
CI: chemical ionisation

DCC: N,N-dicyclohexylcarbodiimide

DCI: desorption chemical ionisation

DIP: diisopropylether

DME: dimethoxyethane

DMF: N,N-dimethylformamide

EE: ethyl acetate

ESI: electron spray ionisation

FAB: fast atom bombardment

n-H: n-heptane

HOBt: 1-hydroxybenzotriazole

MeOH: methanol

MTB: methyl-tert.-butylether

RT: room temperature

THF: tetrahydrofuran

Totu: O-[cyano(ethoxycarbonyl)methyleneamino]-1,1,3,3-tetramethyluronium tetrafluoroborate

The invention is explained by the examples below.

Example 1

2-(1-(4-t-Butyloxycarbonylaminomethylbenzyl)-pyrrolidin-2-yl)-3-naphthalen-2-yl propionic acid ethyl ester

a) 2-(Pyrrolidin-2-ylidene)-3-(naphthyl-2-yl) propionic acid ethyl ester

Sodium hydride (4.5 g of a 60% suspension in mineral oil) was added at 0°C under argon to pyrrolidin-2-ylidene acetic acid ethyl ester (18 g, 116 mmol) in DME (500 ml). After addition was complete, the cooling was removed and after 40 min. 2-bromomethylnaphthalene (228 g, 103 mmol) was slowly added dropwise at RT. After 2 h, H_2O (300 ml) was added and concentrated in a vacuum. The residue is adjusted to pH 7 with 4 n HCl and extracted three times with ethyl acetate, dried ($MgSO_4$) and evaporated. Following chromatography on SiO_2 with EE/H 1/2 as eluent, the title compound was obtained as an oil.

R_f (EE/n-H 1/1) = 0.5.
MS (DCI) = 296 (M + H).

b) 4-t-Butyloxycarbonylaminomethyl benzyl alcohol

4-Aminomethylbenzoic acid (24 g, 159 mmol) was added under argon to a suspension of sodium borohydride (15 g, 428 mmol) in DME (800 ml). A solution of iodine (40.6 g, 159 mmol) in DME (150 ml) was then added dropwise at 6-10°C, the solution foaming greatly in the process. After addition was complete, the solution was allowed to act for 2 h without cooling, then boiled under reflux for 18 h. After cooling to RT methanol (100 ml) was added dropwise, the suspension foaming greatly initially. The mixture was then evaporated in a vacuum and 20% aqueous KOH (300 ml) added. After 18 h at RT, extraction was performed three times with MTB (3 x 300 ml). The organic phases were washed once with saturated NaCl solution, dried ($MgSO_4$) and concentrated in a vacuum. To the resultant alcohol (14 g , 102 mmol) in THF (150 ml) there was added diisopropylethylamine (17.5 ml, 107 mmol) and pyrocarboxylic acid di-t-butylester (22 g, 107 mmol) dissolved in THF (100 ml) at RT. After 18 h the mixture was evaporated in a vacuum and taken up in ethyl acetate. The organic phase was washed once with 5% $NaHSO_4$, saturated Na_2CO_3 and NaCl solutions respectively, dried over $MgSO_4$ and concentrated in a vacuum. The residue was stirred with n-heptane (100 ml), suction filtered and washed with n-heptane (200 ml), the title compound being obtained as a colourless powder.
R_f (EE/n-H 2/1) = 0.45.
^{1}H-NMR ($CdCl_3$) δ = 7.25 (m, 4H), 4.8 (s(broad), 1H), 4.65 (m, 2H), 4.3 (d, J=6.0 Hz, 2H), 1.25 (s, 9H).

c) (4-t-Butyloxycarbonylaminomethylbenzyl) methane sulphonate

Mesyl chloride (5.0 ml, 50 mmol) was added dropwise at 0°C to the title compound of 1b (10 g, 30 mmol) and triethylamine (8.7 ml, 63 mmol) in THF (100 ml). After 1 h the mixture was adjusted to pH 7 and evaporated in a vacuum. Ethyl acetate (300 ml) was then added and washing performed once with each of 5% $NaHSO_4$, saturated Na_2HCO_3 and NaCl solutions, dried ($MgSO_4$) and again concentrated, the title compound being obtained as an oil.

R_f (EE/n-H 2/1) = 0.6.

^{1}H-NMR ($CdCl_3$) δ = 7.35 (m, 4H), 5.2 (s, 2H), 4.85 (s broad, 1H), 4.3 (d, J=6 Hz, 2H), 2.9 (s, 3H), 1.2 (s, 9H).

d) 2-(1-(4-t-Butyloxycarbonylaminomethylbenzyl)pyrrolidin-2-ylidene)-3-naphthyl-2-yl propionic acid ethyl ester

Sodium hydride (2.7 g; 60% in mineral oil) was added to the title compound according to Example 1a (9.8 g, 33 mmol) in DMF (150 ml) at 5°C. After addition was complete the mixture was stirred for 30 min without cooling and the title compound of 1c (10.5 g, 33 mmol) dissolved in DMF (10 ml) added dropwise. After 2 h at RT, H_2O (20 ml) was added and evaporation undertaken in a vacuum. H_2O (200 ml) was added to the residue and the latter extracted three times with 200 ml ethyl acetate on each occasion. The organic extracts were dried ($MgSO_4$) and concentrated in a vacuum. Chromatography on SiO_2 with EE/H 1/1 as eluent produced the title compound as an oil.

R_f (EE/n-H 1/1) = 0.4. MS (DCI) = 515 (M + H).

e) 2-(1-(4-t-Butyloxycarbonylaminomethylbenzyl)pyrrolidin-2-yl)-3-naphthalene-2-yl propionic acid ethyl ester

Sodium cyanoborohydride (25 mg, 0.39 mmol) and a spatula tip of bromocresol green were added to the title compound according to Example 1d (200 mg, 0.39 mmol) in methanol (6 ml) at RT. The pH was then adjusted to its point of change with 0.1 n HCl. After 18 h the solution was evaporated and H_2O (20 ml) added. The pH was adjusted to 10 and extracted twice with MTB (100 ml). The organic phase was dried ($MgSO_4$) and concentrated in a vacuum, the title compound being obtained as an oil.

R_f (EE/MeOH 5/1) = 0.2.

M (DCI) = 517 (M + H).

Example 2

2-(1-(4-Aminomethylbenzyl)pyrrolidin-2-ylidene)-3-naphthyl-2-yl propionic acid ethyl ester · Trifluoroacetate

Trifluoroacetic acid (10 ml) was added at 0°C to the title compound according to Example 1d (14 mg, 1 mmol) in dichloromethane (10 ml). After 4 h the solution was evaporated and digested twice with DIP (10 ml) and freeze-dried, the title compound being obtained as an amorphous powder.

R_f (CH_2Cl_2/MeOH/CH_3CO_2H/H_2O 130/30/5/5) = 0.3.

MS (ESI) = 415 (M + H).

Example 3

2-(1-(4-Aminomethylbenzyl)pyrrolidin-2-yl)-3-naphthalen-2-yl propionic acid ethyl ester · Ditrifluoroacetate

The title compound according to Example 1 (516 mg, 1 mmol) was reacted in a similar manner to Example 2, the title compound being obtained as an amorphous powder.

R_f (CH_2Cl_2/MeOH/CH_3CO_2H/H_2O 130/30/5/5) = 0.15.

MS (ESI) = 417 (M + H).

Example 4

2-(1-(4-Guanidinomethylbenzyl)pyrrolidin-2-ylidene)-3-naphthalen-2-yl propionic acid ethyl ester

1H-Pyrazole-1-carboxamidine hydrochloride (150 mg, 1.0 mmol) was added at RT to the title compound according to Example 2 (528 mg, 1 mmol) in DMF (20 ml) and diisopropylethylamine (0.44 ml, 2.6 mmol). After 18 h the product was precipitated out by the addition of DIP (100 ml).

R_f (CH_2Cl_2/MeOH/CH_3CO_2H/H_2O 130/30/5/5) = 0.4.

MS (ESI) = 457 (M + H).

Example 5

2-(1-(4-Guaninomethylbenzyl)pyrrolidin-2-yl)-3-naphthalen-2-yl propionic acid ethyl ester

The title compound according to Example 3 (530 mg, 1 mmol) was reacted similar to the title compound according to Example 4, to form the title compound according to Example 5.

R_f (CH_2Cl_2/MeOH/CH_3CO_2H/H_2O 130/30/5/5) = 0.2.

MS (ESI) = 459 (M + H).

Example 6

2-(1-(4-((1-(8-Aminooctylcarbamoyl)-4-phenylpiperidine-4-carbonyl)-L-β-(2-thienyl)alaninyl)aminomethylbenzyl)pyrrolidin-2-ylidene)-3-naphthalen-2-yl propionic acid ethyl ester · Trifluoroacetate

a) 4-Phenylpiperidine-4-carboxylic acid methyl ester

4-Phenylpiperidine-4-carboxylic acid tosylate (200 g, 0.53 mol) was boiled in methanol (1000 ml) with the addition of thionyl chloride (150 ml). After the evolution of HCl was complete, the mixture was evaporated. A pH of around 11 was adjusted with saturated Na_2CO_3 solution and extraction with ethyl acetate performed three times (3 x 300 ml). After drying the organic phases over $MgSO_4$ they were concentrated in a vacuum, the product being obtained as an oil.

R_f (EE/MeOH 10/1) = 0.4.

MS (DCI) = 220 (M + H).

b) 1-(8-tert.-Butyloxycarbonylaminooctylcarbamoyl)-4-phenylpiperidine-4-carboxylic acid methyl ester

N,N'-Carbonyldiimidazole (5.8 g, 35 mmol) was added at RT to 8-Boc-aminooctyl-amine hydrochloride (10 g, 35 mmol) and diisopropylethylamine (4.6 g, 35 mmol) in DMF (100 ml). After 4 h the compound according to Example 1a (7.8 g, 35 mmol)

was added and stirred for a further 18 hours at RT. Ethyl acetate (500 ml) was then added and washing performed once (100 ml) with each of 5% $NaHSO_4$, saturated Na_2CO_3 and saturated NaCl solution. The organic phase was dried over $MgSO_4$ and concentrated in a vacuum.

Yield of compound 1b): 15 g.

R_f (EE) = 0.6.

MS (FAB) = 490 (M + H).

c) 1-(8-tert.-Butyloxycarbonylaminooctylcarbamoyl)-4-phenylpiperidine-4-carboxylic acid

The title compound according to Example 1b (15 g, 31 mmol) was stirred in MeOH/H_2O 2/1 (300 ml) and sodium hydroxide (4.8 g, 120 mmol) for 18 h at RT. The solution was then concentrated in a vacuum and adjusted to pH 3 with 1 n HCl. Extraction with 100 ml ethyl acetate was then performed three times. The combined organic extracts were dried over $MgSO_4$. The title compound was obtained by concentrating in a vacuum.

MS (DCI) = 476 (M + H).

d) 1-(8-tert.-Butyloxycarbonylaminooctylcarbamoyl)-4-phenylpiperidine-4-carbonyl-β-(2-thienyl)alanine methyl ester

HOBt (6 g, 44 mmol) and DCC (7.2 g, 35 mmol) were added at RT to the compound according to Example 1c (14 g, 29 mmol) in DMF (100 ml). After 30 min. β-(2-thienyl)alanine methyl ester hydrochloride (6.1 g, 29 mmol) and triethylamine (3 g, 29 mmol) were added. After 18 h the mixture was filtered and the filtrate diluted with ethyl acetate (500 ml). The organic phase was washed once (100 ml) with each of 5% $NaHSO_4$, saturated Na_2CO_3 and saturated NaCl solution, dried over $MgSO_4$ and concentrated in a vacuum. The title compound was obtained after chromatography on SiO_2 with MTB as solvent.

R_f (MTB) = 0.4.

MS (FAB) = 643 (M + H).

e) 1-(8-tert.-Butyloxycarbonylaminooctylcarbamoyl)-4-phenylpiperidine-4-carbonyl-β-(2-thienyl)alanine

The title compound according to Example 1d (12.8 g, 27 mmol) in MeOH/H_2O 2/1 (300 ml) and sodium hydroxide (4.4 g, 110 mmol) were reacted in a manner similar to Example 1c, to obtain the title compound.
MS (FAB) = 629 (M + H).

f) 2-(1-(4-((8-Butyloxycarbonylaminooctylcarbamoyl)-4-phenylpiperidine-4-carbonyl)-L-β-(2-thienyl)alaninyl)aminomethylbenzyl)pyrrolidin-2-yliden)-3-naphthalen-2-yl propionic acid ethyl ester

HOBt (65 mg, 0.48 mmol) and DCC (72 mg, 0.35 mmol) were added at RT to the title compound according to Example 6e (200 mg, 0.32 mmol) in DMF (5 ml). After 1 h the title compound according to Example 2 (170 mg, 0.31 mmol) and triethylamine (43 ml, 0.31 mmol) were added. After 18 h the mixture was concentrated in a vacuum. Acetonitrile was added to the residue and filtered. The filtrate was again concentrated. After adding ethyl acetate (50 ml) it was washed once (50 ml) with each of saturated Na_2CO_3 and NaCl solutions, dried ($MgSO_4$) and concentrated in a vacuum. Chromatography on SiO_2 produced the title compound (eluent EE).
R_f (EE) = 0.45.
MS (ESI) = 1026 (M + H).

g) 2-(1-(4-((1-(8-Aminooctylcarbamoyl)-4-phenylpiperidine-4-carbonyl)-L-β-(2-thienyl)alaninyl)aminomethylbenzyl)pyrrolidin-2-ylidene)-3-naphthalen-2-yl propionic acid ethyl ester · Trifluoroacetate

The title compound according to Example 6f (150 mg, 0.15 mmol) was reacted in a similar manner to Example 2, the title compound according to Example 6 being obtained as an oil.
R_f (CH_2Cl_2/MeOH/CH_3CO_2H/H_2O 130/30/5/5) = 0.35.
MS (ESI) = 925 (M + H).

Example 7

2-(1-(4-((1-(8-Aminooctylcarbamoyl)-4-phenylpiperidine-4-carbonyl)-L-β-(2-thienyl)alaninyl)aminomethylbenzyl)pyrrolidin-2-yl)-3-naphthalen-2-yl propionic acid ethyl ester

The title compound was obtained by reacting the title compound according to Example 6 (120 mg, 0.13 mmol) in a similar manner to Example 1e.
R_f (CH_2Cl_2/MeOH/CH_3CO_2H/H_2O 130/30/5/5) = 0.3.
MS (FAB) = 927 (M + H).

Example 8

2-(1-(4-(1-(8-t-Butyloxycarbonylaminooctylcarbamoyl)-4-phenylpiperidine-4-carbonyl)aminomethylbenzyl)pyrrolidin-2-ylidene)-3-naphthalen-2-yl propionic acid ethyl ester

The title compound was obtained from the title compound according to Example 2 (170 mg, 0.32 mmol) and the title compound according to Example 6c (150 mg, 0.32 mmol) in a manner similar to Example 6d.
R_f (EE) = 0.3.
MS (ESI) = 872 (M + H).

Example 9

2-(1-(4-(1-(8-t-Butyloxycarbonylaminooctylcarbamoyl)-4-phenylpiperidine-4-carbonyl)aminomethylbenzyl)pyrrolidin-2-yl)-3-naphthalen-2-yl propionic acid ethyl ester

The title compound was obtained from the title compound according to Example 8 (285 mg, 0.33 mmol) by means of a reaction similar to Example 1e.
R_f (EE/MeOH 1/1) = 0.3.
MS (FAB) = 874 (M + H).

Example 10

2-(1-(4-(1-(8-Aminooctylcarbamoyl)-4-phenylpiperidine-4-carbonyl)aminomethylbenzyl)pyrrolidin-2-ylidene)-3-naphthyl-2-yl propionic acid ethyl ester · Trifluoroacetate

The title compound was obtained from the title compound according to Example 8 (120 mg, 0.14 mmol) by means of a reaction similar to Example 2.
R_f (CH_2Cl_2/MeOH/CH_3CO_2H/H_2O 130/20/5/5) = 0.5.
MS (FAB) = 772 (M + H).

Example 11

2-(1-(4-(1-(8-Aminooctylcarbamoyl)-4-phenylpiperidine-4-carbonyl)aminomethylbenzyl)pyrrolidin-2-yl)-3-naphthyl-2-yl propionic acid ethyl ester · Ditrifluoroacetate

The title compound was obtained from the title compound according to Example 9 (120 mg, 0.14 mmol) by means of a reaction similar to Example 2.
R_f (CH_2Cl_2/MeOH/CH_3CO_2H/H_2O 130/30/5/5) = 0.3.
MS (FAB) = 774 (M + H).

Example 12

2-(1-(4-(1-(8-Guanidinooctylcarbamoyl)-4-phenylpiperidine-4-carbonyl)aminomethylbenzyl)pyrrolidin-2-ylidene)-3-naphthyl-2-yl propionic acid ethyl ester · Trifluoroacetate

The title compound was obtained from the title compound according to Example 10 (120 mg, 0.14 mmol) by means of a reaction similar to Example 4.
R_f (CH_2Cl_2/MeOH/CH_3CO_2H/H_2O 130/20/5/5) = 0.5.
MS (FAB) = 814 (M + H).

Example 13

2-(1-(4-(1-(8-Guanidinooctylcarbamoyl)-4-phenylpiperidine-4-carbonyl)aminomethylbenzyl)pyrrolidin-2-yl)-3-naphthyl-2-yl propionic acid ethyl ester · Trifluoroacetate

The title compound was obtained from the title compound according to Example 11 (120 mg, 0.14 mmol) by means of a reaction similar to Example 4.

R_f (CH_2Cl_2/MeOH/CH_3CO_2H/H_2O 130/20/5/5) = 0.25.

MS (FAB) = 816 (M + H).

Example 14

2-(1-(4-(1-(6-Aminohexylcarbamoyl)-4-phenylpiperidine-4-carbonyl)aminomethylbenzyl)pyrrolidin-2-ylidene)-3-naphthyl-2-yl propionic acid ethyl ester · Trifluoroacetate

The title compound was obtained from the title compound according to Example 2 (350 mg, 0.67 mmol) and 1-(6-t-butyloxycarbonylaminohexylcarbamoyl)-4-phenyl-piperidine-4-carboxylic acid (300 mg, 0.67 mmol) by means of a reaction similar to Examples 6d and 2.

R_f (CH_2Cl_2/MeOH/CH_3CO_2H/H_2O 130/30/5/5) = 0.5.

MS (FAB) = 744 (M + H).

Example 15

2-(1-(4-(1-(6-Aminohexylcarbamoyl)-4-phenylpiperidine-4-carbonyl)aminomethylbenzyl)pyrrolidin-2-yl)-3-naphthyl-2-yl propionic acid ethyl ester

The title compound was obtained from the title compound according to Example 14 (120 mg, 0.14 mmol) by means of a reaction similar to Example 1e.

R_f (CH_2Cl_2/MeOH/CH_3CO_2H/H_2O 130/20/5/5) = 0.25.

MS (FAB) = 776 (M + H).

Example 16

2-(1-(4-(1-(6-Guanidinohexylcarbamoyl)-4-phenylpiperidine-4-carbonyl)aminomethylbenzyl)pyrrolidin-2-yl)-3-naphthyl-2-yl propionic acid ethyl ester

The title compound was obtained from the title compound according to Example 15 (250 mg, 0.29 mmol) by means of a reaction similar to Example 4.

R_f (CH_2Cl_2/MeOH/CH_3CO_2H/H_2O 130/30/5/5) = 0.1.

MS (ESI) = 788 (M + H).

Example 17

1-(4-Aminomethylbenzyl)-2,3,3a,4,5,6-hexahydroindole-7-carboxylic acid ethyl ester · Trifluoroacetate

a) 2,2-Dimethyl-5-(3-allyl-pyrrolidin-2-ylidene)-[1,3]-dioxane-4,6-dione

n-Butyllithium (24 ml of a 15% solution in hexane) was added to 2,2-dimethyl-5-pyrrolidin-2-ylidene-[1,3]-dioxane-4,6-dione (3 g, 13.5 mmol) in dry THF (120 ml) under an argon atmosphere at -65°C. The cooling was then removed and after 45 min. it was cooled down again to -65°C. Allyl bromide (1.2 ml, 13.9 mmol) was injected into this suspension. After 30 min. 30 ml of 10% HCl solution was added and extracted three times with ethyl acetate (3 x 100 ml). The combined organic extracts were washed once with saturated NaCl solution (100 ml), dried ($MgSO_4$) and concentrated in a vacuum, the title compound being obtained as colourless amorphous crystals.

R_f (EE/n-H 2/1) = 0.5.

MS (Cl) = 251 (M^+).

b) 3-Allylpyrrolidin-2-ylidene acetic acid ethyl ester

The title compound according to Example 17a (3.2 g, 12.7 mmol) in ethanol (60 ml; absolute) and sodium methylate (16.5 ml of a 1M solution in absolute ethanol) was boiled under reflux for 18 h. The mixture was then concentrated, H_2O (30 ml) added and the pH adjusted to 5-6 with 2N HCl. Extraction was then undertaken with ethyl acetate (100 ml) twice, the organic extracts dried ($MgSO_4$) and concentrated in a vacuum. The title compound was obtained as an oil.

R_f (EE/n-H 2/1) = 0.6.

MS (Cl) = 195 (M^+).

c) 5-Iodo-2,3,3a,4,5,6-hexahydro-1H-indole-7-carboxylic acid ethyl ester

A solution of N-iodosuccinimide (6.9 g, 30 mmol) in dichloromethane (100 ml) was added dropwise to the title compound according to Example 17b (5, 1 g, 23 mmol) in dichloromethane (100 ml) under argon at -5°C. The cooling was removed after 3 h (during which time there formed (3-allylpyrrolidin-2-ylidene)-2-iodoacetic acid ethyl ester). After 18 h at RT washing was performed once with semi-saturated Na_2SO_3 solution (100 ml) and once with H_2O (100 ml). The organic phase was dried ($CaCl_2$) and concentrated in a vacuum. The crystalline residue was crystallised from ethanol.

R_f (EE/n-H 1/2) = 0.25.

MS (ESI) = 322 (M + H).

d) 2,3,3a,4,5,6-Hexahydro-1H-indole-7-carboxylic acid ethyl ester

The title compound according to Example 17c (500 mg, 1.56 mmol) and Raney nickel (100 mg) were stirred in a mixture of methanol (5 ml), THF (10 ml) and diisopropyl-ethylamine (2 ml) in a hydrogen atmosphere (1 atm) for 1 h. The mixture was then filtered off from the catalyst over kieselguhr, saturated NaCl solution (50 ml) was added and extraction performed twice with ethyl acetate. The organic extracts were dried ($MgSO_4$) and concentrated in a vacuum, the title compound being obtained in crystalline form.

R_f (DIP) = 0.6. MS (El) = 196 (M + H).

Melting point: 74°C (crystallised from DIP).

e) 1-(4-t-Butyloxycarbonylaminomethylbenzyl)-2,3,3a,4,5,6-hexahydroindole-7-carboxylic acid ethyl ester

The title compound was obtained from the title compound according to Example 1c (1.05 g, 3.3 mmol) and the title compound according to Example 17d (640 mg, 3.3 mmol) by means of a reaction similar to Example 1d.
R_f (E/n-H 1/4) = 0.1.
MS (ESI) = 415 (M + H).

f) 1-(4-Aminomethylbenzyl)-2,3,3a,4,5,6-hexahydroindole-7-carboxylic acid ethyl ester · Trifluoroacetate

The title compound according to Example 17 was obtained from the title compound according to Example 17e (200 mg, 0.48 mmol) by means of a reaction similar to Example 2.
R_f (CH_2Cl_2/MeOH/CH_3CO_2H/H_2O 130/30/5/5) = 0.3.
MS (ESI) = 315 (M + H).

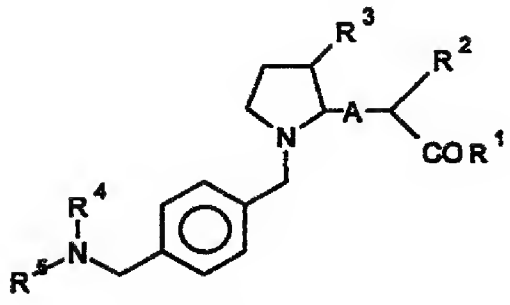
Example 18

1-(4-Aminomethylbenzyl)octahydroindole-7-carboxylic acid ethyl ester · Trifluoroacetate

The title compound was obtained from the title compound according to Example 17e (414 mg, 1 mmol) by means of a reaction similar to Examples 1e and 2.
R_f (CH_2Cl_2/MeOH/CH_3CO_2H/H_2O 130/30/5/5) = 0.4.
MS (ESI) = 317 (M + H).

Claims

1. Compounds of the formula (I)



(I)

wherein the symbols have the following meaning:

a) R^1 stands for

1. –OH,
2. –O–(C_1-C_{10})-alkyl,
3. –O–(C_3-C_6)-alkenyl,
4. –O–(C_6-C_{10})-aryl-(C_1-C_3)-alkyl,
5. $-NR^6R^7$;

b) R^2 stands for

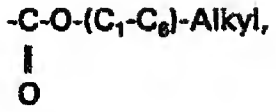
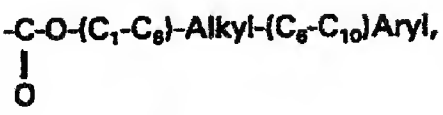
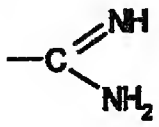
1. (C_1-C_{10})-alkyl,
2. (C_2-C_{10})-alkenyl,
3. (C_3-C_{10})-alkinyl,
4. (C_6-C_{10})-aryl-(C_1-C_3)-alkyl,
5. (C_3-C_8)-cycloalkyl,
6. (C_4-C_{10})-cycloalkyl-(C_1-C_4)-alkyl,
7. (C_5-C_{10})-cycloalkyl-(C_2-C_4)-alkenyl,
8. (C_5-C_{10})-cycloalkyl-(C_2-C_4)-alkinyl,
9. $-(CH_2)_m-B-(CH_2)_n-R^5$,
10. (C_6-C_{10})-aryl,
11. a residue as defined in b) 1., 2., 3. or 9. which is monosubstituted with COR^1,
12. a residue as defined in b) 1., 2., 3. or 9. wherein one to all the H atoms are substituted by halogen, or

13. the residue defined in b) 4. and 10. substituted on the aryl by 1 or 2 of the same or different residues from the series halogen, (C_1-C_4)-alkoxy and nitro, cyano;

c) R^3 stands for

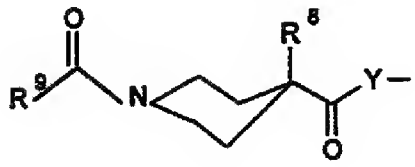
1. hydrogen,
2. (C_1-C_8)-alkyl,
3. (C_3-C_8)-cycloalkyl,
4. (C_6-C_{10})-aryl-(C_1-C_3)-alkyl,
5. (C_2-C_6)-alkenyl,
6. (C_3-C_6)-alkinyl,
7. R^2 and R^3 together stand for (C_2-C_4)-alkyl,
8. a residue as defined in c) 7. which is substituted by halogen;

d) R^4 stands for

1. hydrogen,
2. (C_1-C_6)-alkyl,
3. (C_6-C_{10})-aryl-(C_1-C_3)-alkyl,
4. (C_3-C_{10})-alkenyl,
5. 
6. 
7. 

e) R^5 stands for

1. hydrogen,
2. a residue of the formula (II)



(II)

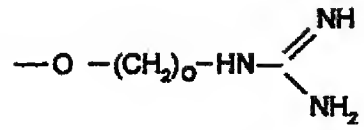
f) R^6 and R^7 are the same or different and stand for

1. hydrogen,
2. (C_1-C_{10})-alkyl,
3. (C_6-C_{10})-aryl-(C_1-C_3)-alkyl,
4. (C_1-C_{10})-alkylamino,
5. (C_1-C_{10})-alkylguanidino;

g) R^8 stands for

1. (C_6-C_{10})-aryl,
2. (C_1-C_6)-alkyl,
3. (C_3-C_8)-cycloalkyl,
4. (C_6-C_{10})-aryl-(C_1-C_3)-alkyl,
5. (C_2-C_6)-alkenyl,
6. a residue defined in g) 1. and 4. which is substituted with one or more residues from the series COR^1, halogen, nitro, cyano, (C_1-C_4)-alkoxy or amino;

h) R^9 stands for

1. $-NH-(CH_2)_o-NHR^4$
2. $-O-(CH_2)_o-NH_2$
3. 

i) A stands for a single or double bond;

j) B is O, NR^3 or S;

k) Y stands for a direct bond or an amino acid, preferably phenylalanine, 2-chlorophenylalanine, 3-chlorophenylalanine, 4-chlorophenylalanine, 2-fluorophenylalanine, 3-fluorophenylalanine, 4-fluorophenylalanine, tyrosine, O-methyltyrosine, β-(2-thienyl)alanine, glycine, cyclohexylalanine, leucine, isoleucine, valine, norleucine or phenylglycine, serine or cysteine;

l) m stands for a number from 1 to 5,

m) n stands for a number from 1 to 5,

n) o stands for a number from 1 to 10,

and physiologically compatible salts thereof.

2. Compounds of the formula I as claimed in claim 1, wherein

a) R^2 stands for

1. $(C_1\text{-}C_6)$-alkyl,
2. $(C_2\text{-}C_6)$-alkenyl,
3. $(C_6\text{-}C_{10})$-aryl-$(C_1\text{-}C_3)$-alkyl,
4. $(C_3\text{-}C_8)$-cycloalkyl,
5. $(C_3\text{-}C_6)$-cycloalkyl-$(C_1\text{-}C_3)$-alkyl,
6. a residue defined in a) 3. and 5. which is substituted with one or more residues from the series halogen, nitro, cyano $(C_1\text{-}C_4)$-alkoxy, COR^1 or amino;

c) R^8 stands for

1. $(C_6\text{-}C_{10})$-aryl,
2. $(C_6\text{-}C_{10})$-aryl-$(C_1\text{-}C_3)$-alkyl,
3. a residue defined in c) 1. and 2. which is substituted with one or more residues from the series halogen, nitro, cyano, $(C_1\text{-}C_4)$-alkoxy, amino or COR^1.

3. Compounds of the formula I as claimed in claims 1 or 2, wherein

a) R^1 stands for $-O-(C_1\text{-}C_{10})$-alkyl;

b) R^2 stands for

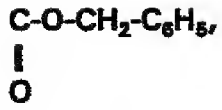
1. $(C_6\text{-}C_{10})$-aryl-CH_2-,
2. $(C_3\text{-}C_8)$-cycloalkyl,
3. $(C_3\text{-}C_8)$-cycloalkyl-CH_2-;

c) R^3 stands for

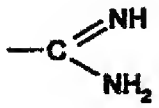
1. $(C_3\text{-}C_5)$-alkenyl,
2. phenyl-$(C_1\text{-}C_3)$-alkyl,
3. R^2 and R^3 together stand for $(C_2\text{-}C_3)$-alkyl;

d) R^4 stands for

1. hydrogen,

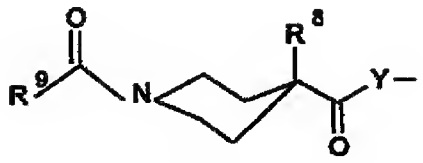
2. 

3. 

4. 

e) R^5 stands for

1. hydrogen,
2. a residue of the formula (II)



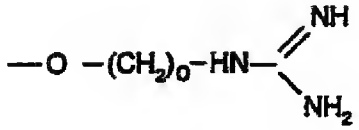
(II)

f) R^8 stands for

1. phenyl,
2. benzyl;

g) R^9 stands for

1. $-NH-(CH_2)_o-NHR^4$,
2. $-O-(CH_2)_o-NH_2$,

3. 

h) A is a single or double bond;

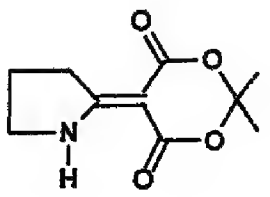
i) Y stands for

1. a single bond,
2. an amino acid from the series phenylalanine, β-(2-thienyl)alanine, O-methyltyrosine, glycine, cyclohexylalanine, leucine, isoleucine, valine, phenylglycine, serine or cysteine;

j) o is a number from 1 to 10.

4. Method for the production of compounds of formula I as claimed in claims 1 to 3, characterised in that

a) a compound of the formula (III)



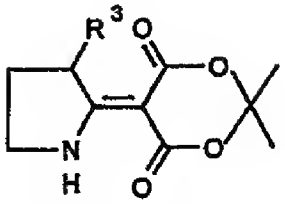
(III)

with a compound R^3–X wherein

R^3 stands for hydrogen, (C_1-C_8)-alkyl, (C_3-C_8)-cycloalkyl, (C_6-C_{10})-aryl-(C_1-C_3)-alkyl, (C_2-C_6)-alkenyl or (C_3-C_6)-alkinyl, and

X stands for a leaving group, such as halogen, mesylate or tosylate,

is reacted with an organometallic base, such as n-butyllithium, s-butyllithium, methyllithium or phenyllithium, sodium amide and alkali-metal salts of organic nitrogen bases, such as lithium diisopropylamide, in an inert solvent such as THF, ether, toluene or dimethoxyethane, preferably at -78°C, to form a compound of the formula IV



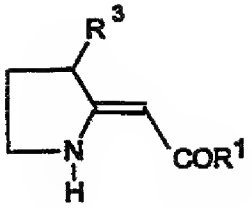
(IV)

wherein R^3 is as defined above;

b) the compound of formula IV is boiled under reflux with an alcoholate of the formula R^1Na or R^1K wherein

R^1 stands for –OH, –O–(C_1-C_{10})-alkyl, –O–(C_3-C_6)-alkenyl or –O–(C_6-C_{10})-aryl-(C_1-C_3)-alkyl,

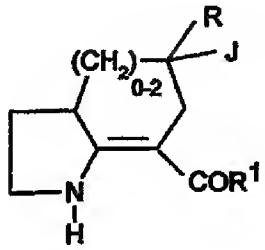
and the corresponding alcohol, a compound of the formula V being obtained



(V)

wherein R^1 and R^3 are as defined above;

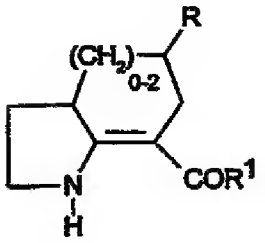
c_1) if in formula I R^2 and R^3 together stand for $(C_2$-$C_4)$-alkyl which may optionally be substituted with halogen and in formula V R^3 stands for $(C_2$-$C_6)$-alkenyl, the compound of formula V is reacted with J_2 or radical-producing reagents in methylene chloride or THF at room temperature to form a compound of the formula VI



(VI)

wherein R stands for hydrogen or $(C_1$-$C_3)$-alkyl and R^1 is as defined in b), and

c_2) the resultant compound of formula VI is reacted with Raney nickel at 1 atm H_2 and diisopropylethylamine as base for 1 hour at room temperature to form a compound of the formula VII

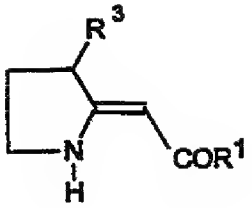


(VII)

wherein R stands for hydrogen or $(C_1$-$C_3)$-alkyl and

R^1 is as defined in b);

d) if in formula I R^2 and R^3 together do not stand for $(C_2$-$C_4)$-alkyl which may optionally be substituted with halogen, a compound of the formula V



(V)

wherein R^1 stands for –O–(C_1-C_{10})-alkyl, –O–(C_3-C_6)-alkenyl or –O–(C_6-C_{10})-aryl-(C_1-C_3)-alkyl and

R^3 stands for hydrogen, (C_1-C_8)-alkyl, (C_3-C_8)-cycloalkyl, (C_6-C_{10})-aryl-(C_1-C_3)-alkyl, (C_2-C_6)-alkenyl or (C_3-C_6)-alkinyl

is deprotonated with a base, e.g. sodium hydride, and is then reacted with a compound R^2–X,

wherein R^2 stands for (C_1-C_{10})-alkyl, (C_2-C_{10})-alkenyl, (C_3-C_{10})-alkinyl, (C_6-C_{10})-aryl-(C_1-C_3)-alkyl, (C_3-C_8)-cycloalkyl, (C_4-C_{10})-cycloalkyl-(C_1-C_4)-alkyl, (C_5-C_{10})-cycloalkyl-(C_2-C_4)-alkenyl, (C_5-C_{10})-cycloalkyl-(C_2-C_4)-alkinyl, -$(CH_2)_m$–B–$(CH_2)_n$–R^5, (C_6-C_{10})-aryl; (C_1-C_{10})-alkyl, (C_2-C_{10})-alkenyl, (C_3-C_{10})-alkinyl or –$(CH_2)_m$–B–$(CH_2)_n$–R^5 which are monosubstituted with COR^1; (C_1-C_{10})-alkyl, (C_2-C_{10})-alkenyl, (C_3-C_{10})-alkinyl or –$(CH_2)_m$–B–$(CH_2)_n$–R^5 wherein one to all the H atoms are substituted by halogen; or (C_6-C_{10})-aryl-(C_1-C_3)-alkyl or (C_6-C_{10})-aryl which are substituted on the aryl with 1 or 2 of the same or different residues from the series halogen, (C_1-C_4)-alkoxy and nitro, cyano,

B is O, NR^3 or S,

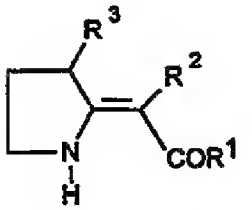
m is a number from 1 to 5,

n is a number from 1 to 5,

R^5 stands for hydrogen or a residue of the formula II, and

X stands for a suitable leaving group, e.g. halogen, mesylate or tosylate,

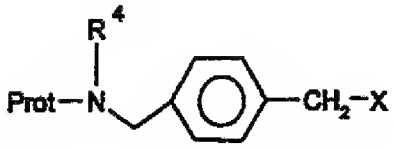
to form a compound of the formula VIII



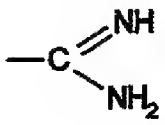
(VIII)

wherein R^1, R^2 and R^3 are as defined in d);

e) the compound of formula VIII with a compound of the formula

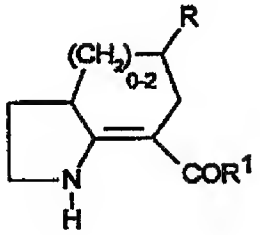


wherein Prot stands for an amino protective group, e.g. tert. butoxycarbonyl, R^4 is hydrogen, $(C_1\text{-}C_6)$-alkyl, $(C_6\text{-}C_{10})$-aryl-$(C_1\text{-}C_3)$-alkyl, $(C_3\text{-}C_{10})$-alkenyl, $-C(O)-O-(C_1\text{-}C_6)$-alkyl, $-C(O)-O-(C_1\text{-}C_6)$-alkyl-$(C_6\text{-}C_{10})$-aryl, or

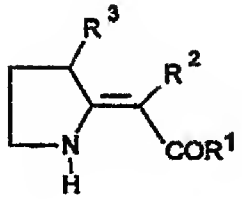


and X stands for a suitable leaving group, e.g. halogen, mesylate or tosylate,

is deprotonated with a base, e.g. sodium hydride, and then reacted with a compound of the formula VII or VIII



(VII)



(VIII)

wherein

R^1 is as defined in d),

R^2 stands for $(C_1\text{-}C_{10})$-alkyl, $(C_2\text{-}C_{10})$-alkenyl, $(C_3\text{-}C_{10})$-alkinyl, $(C_6\text{-}C_{10})$-aryl-$(C_1\text{-}C_3)$-alkyl, $(C_3\text{-}C_8)$-cycloalkyl, $(C_4\text{-}C_{10})$-cycloalkyl-$(C_1\text{-}C_4)$-alkyl, $(C_5\text{-}C_{10})$-cycloalkyl-$(C_2\text{-}C_4)$-alkenyl, $(C_5\text{-}C_{10})$-cycloalkyl-$(C_2\text{-}C_4)$-alkinyl, $-(CH_2)_m-B-(CH_2)_n-R^5$, $(C_6\text{-}C_{10})$-aryl; $(C_1\text{-}C_{10})$-alkyl, $(C_2\text{-}C_{10})$-alkenyl, $(C_3\text{-}C_{10})$-alkinyl or $-(CH_2)_m-B-(CH_2)_n-R^5$ which are monosubstituted with COR^1; $(C_1\text{-}C_{10})$-alkyl, $(C_2\text{-}C_{10})$-alkenyl, $(C_3\text{-}C_{10})$-alkinyl or $-(CH_2)_m-B-(CH_2)_n-R^5$ wherein one to all the H atoms are substituted by halogen; or $(C_6\text{-}C_{10})$-aryl-$(C_1\text{-}C_3)$-alkyl or $(C_6\text{-}C_{10})$-aryl which are substituted on the aryl with 1 or 2 of the same or different residues from the series halogen, $(C_1\text{-}C_4)$-alkoxy and nitro, cyano,

B is O, NR^3 or S,

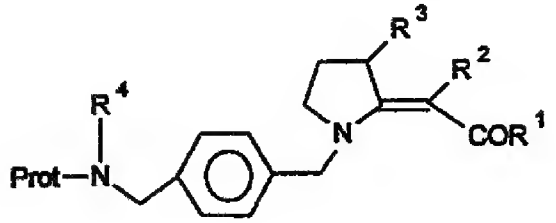
m is a number from 1 to 5,

n is a number from 1 to 5,

R^5 stands for hydrogen or a residue of the formula II, and

R^3 stands for hydrogen, $(C_1\text{-}C_8)$-alkyl, $(C_3\text{-}C_8)$-cycloalkyl, $(C_6\text{-}C_{10})$-aryl-$(C_1\text{-}C_3)$-alkyl or $(C_3\text{-}C_6)$-alkinyl,

to form a compound of the formula IX



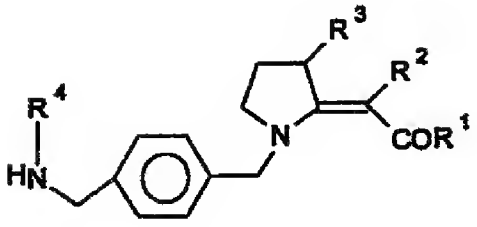
(IX)

wherein R^1, R^2, R^3, R^4 and Prot are as defined in e) and

R^2 and R^3 together stand for $(C_2\text{-}C_4)$-alkyl optionally substituted with halogen;

f) the amino protective group Prot is cleaved off by known methods, e.g. with tert. butoxycarbonyl (Boc) under acidic conditions, preferably in trifluoroacetic acid (TFA) or with HCl in dimethoxyethane, or with TFA in dimethoxyethane or dichloromethane as preferred solvent;

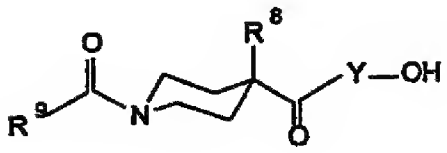
g) optionally the resultant compound of formula X with a free amino group



(X)

wherein R^1, R^2, R^3 and R^4 are as defined in e) (formula IX),

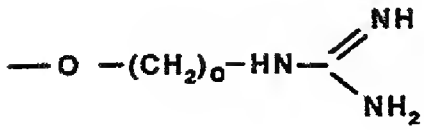
is coupled according to the general methods of peptide chemistry with a compound of the formula II'



(II')

wherein R^8 stands for $(C_6\text{-}C_{10})$-aryl, $(C_1\text{-}C_6)$-alkyl, $(C_3\text{-}C_8)$-cycloalkyl, $(C_6\text{-}C_{10})$-aryl-$(C_1\text{-}C_3)$-alkyl, $(C_2\text{-}C_6)$-alkenyl; $(C_6\text{-}C_{10})$-aryl or $(C_6\text{-}C_{10})$-aryl-$(C_1\text{-}C_3)$-alkyl substituted with one or more residues from the series COR^1, halogen, nitro, cyano, $(C_1\text{-}C_4)$-alkoxy or amino,

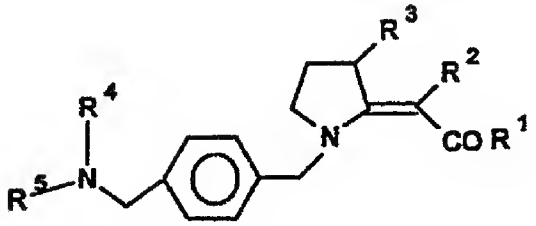
R^9 stands for $–NH–(CH_2)_o–NHR^4$, $–O–(CH_2)_o–NH_2$ or



o is a number from 1 to 10, and

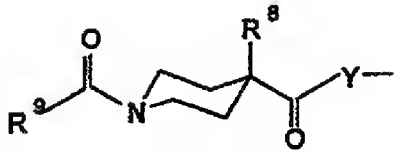
Y stands for a direct bond or an amino acid,

so that a compound of formula X' is obtained



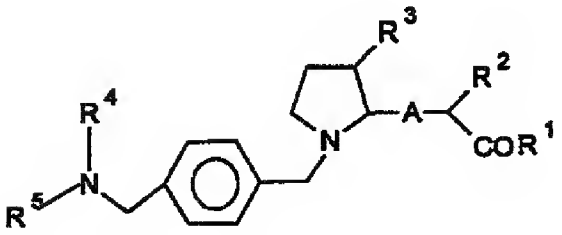
(X')

wherein R^1, R^2, R^3 and R^4 are as defined in g) and R^5 stands for



wherein R^8, R^9 and Y are as defined in g);

h) optionally the double bond of the formulae X and X' is hydrogenated with sodium cyanoborohydride in lower alcohols, such as methanol, at room temperature and around pH 5 to a compound of the formula XI



(XI)

wherein R^1, R^2, R^3, R^4 and R^5 are as defined in g) and

A stands for a single bond;

i) optionally the compounds of the formulae X, X' or XI are saponified under acidic or basic conditions or are heated with HNR^6R^7,

wherein R^6 and R^7 are the same or different and stand for hydrogen, (C_1-C_{10})-alkyl, (C_6-C_{10})-aryl-(C_1-C_3)-alkyl, (C_1-C_{10})-alkylamino or (C_1-C_{10})-alkylguanidino,

in high-boiling solvents, e.g. xylene or DMF, the compounds of formula I being obtained; and

k) the compounds of the formula I are optionally converted by known methods to their physiologically compatible salts.

5. Use of the compounds of formula I as claimed in claims 1 to 3 as therapeutic agents.

6. Therapeutic agents containing a compound of the formula I as claimed in claims 1 to 3.